Targeting IL-6 as a key molecule in the pathogenesis of inflammatory rheumatic diseases

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DISCLOSURES

Frank Buttgereit received consultancy fees, honoraria and/or travel expenses from Horizon Pharma, Mundipharma, and Roche, and grant or study support from Mundipharma.

Agenda

Interleukin 6 (IL-6)

- Biological activities & effects in rheumatoid arthritis (RA)
- IL-6 inhibition for the treatment of RA, giant cell arteritis (GCA) and polymyalgia rheumatica (PMR)

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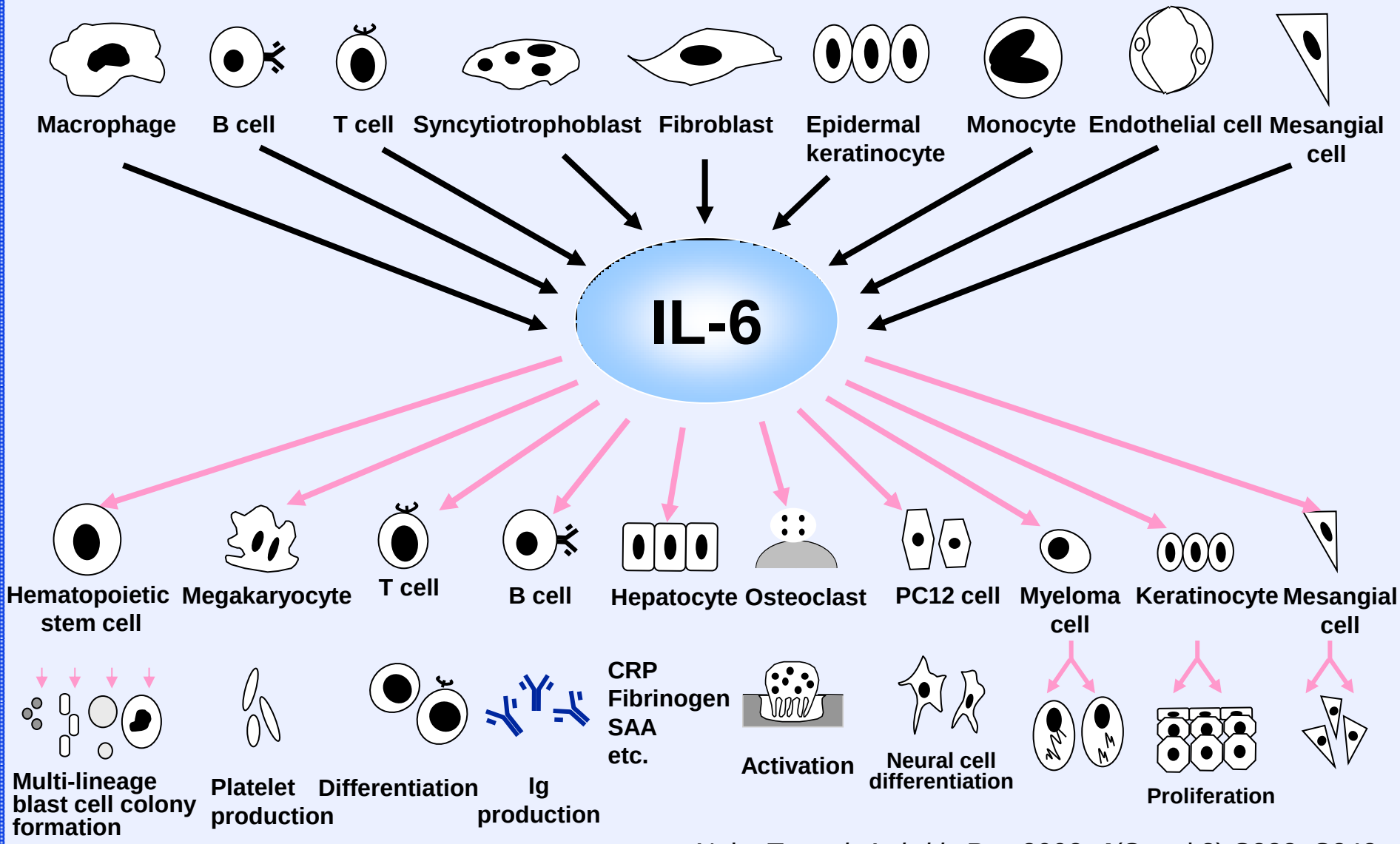
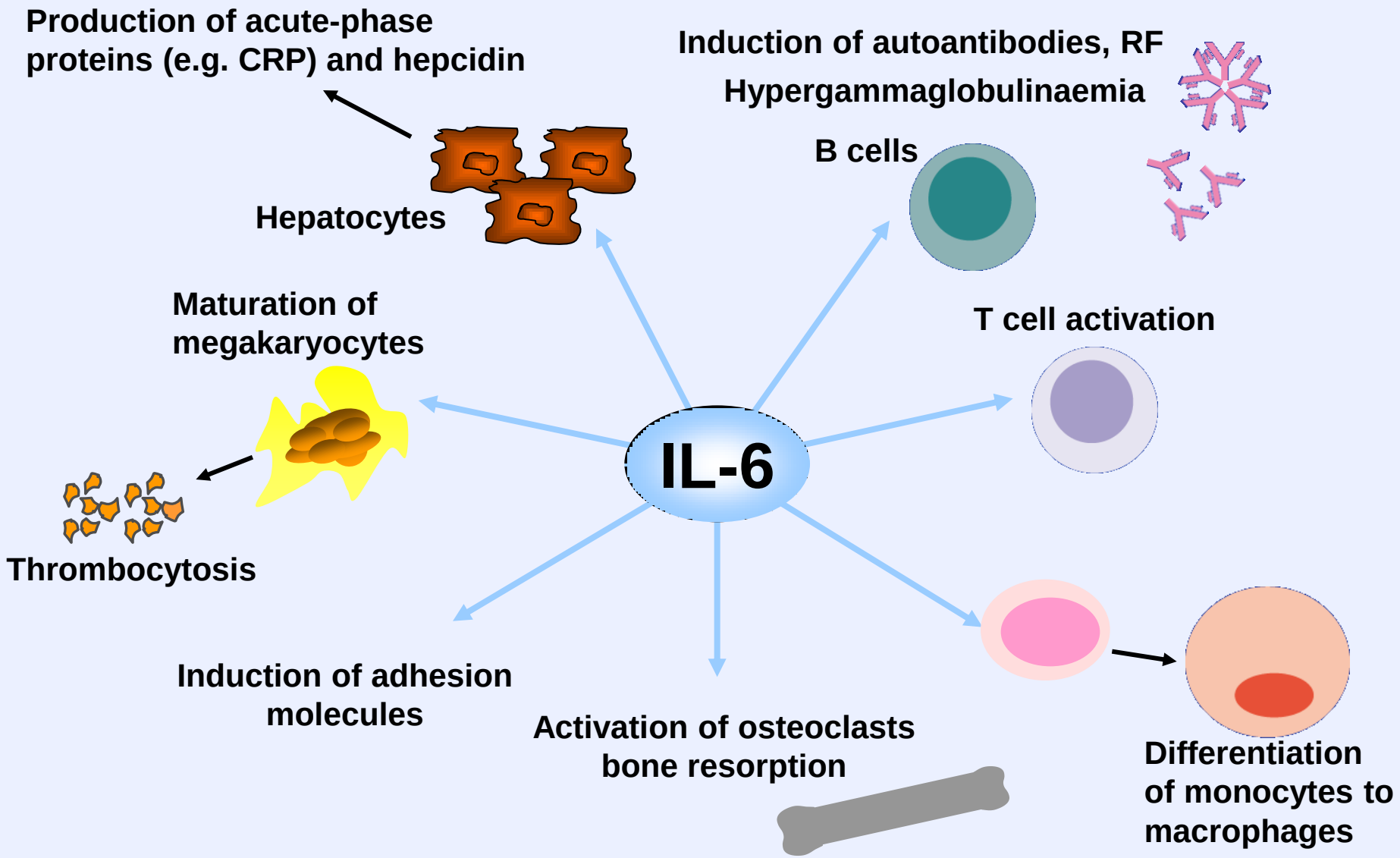
IL-6: Multiple sources and targets



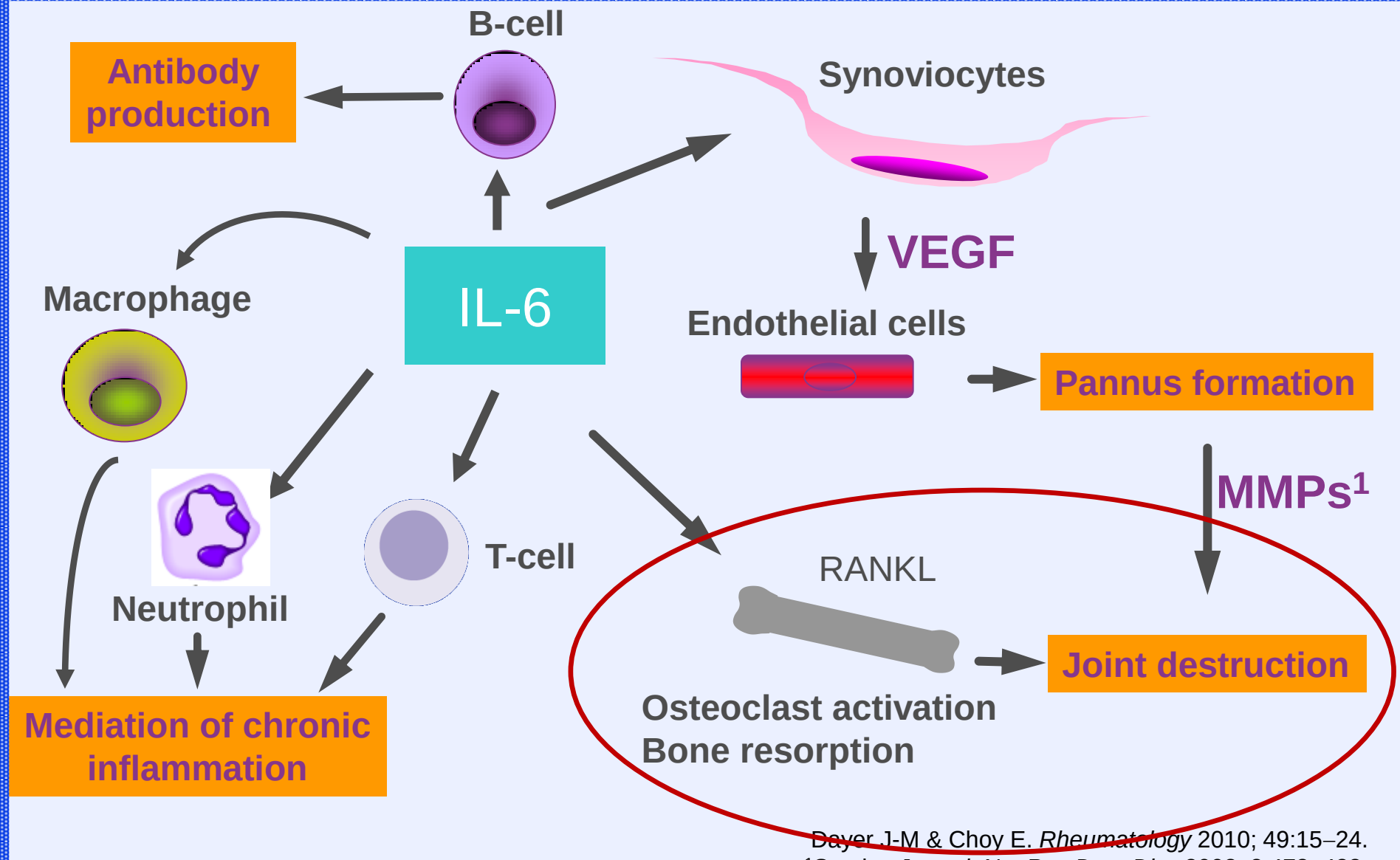
Naka T, *et al. Arthritis Res* 2002; **4**(Suppl 3):S233–S242.

IL-6: Important biological activities



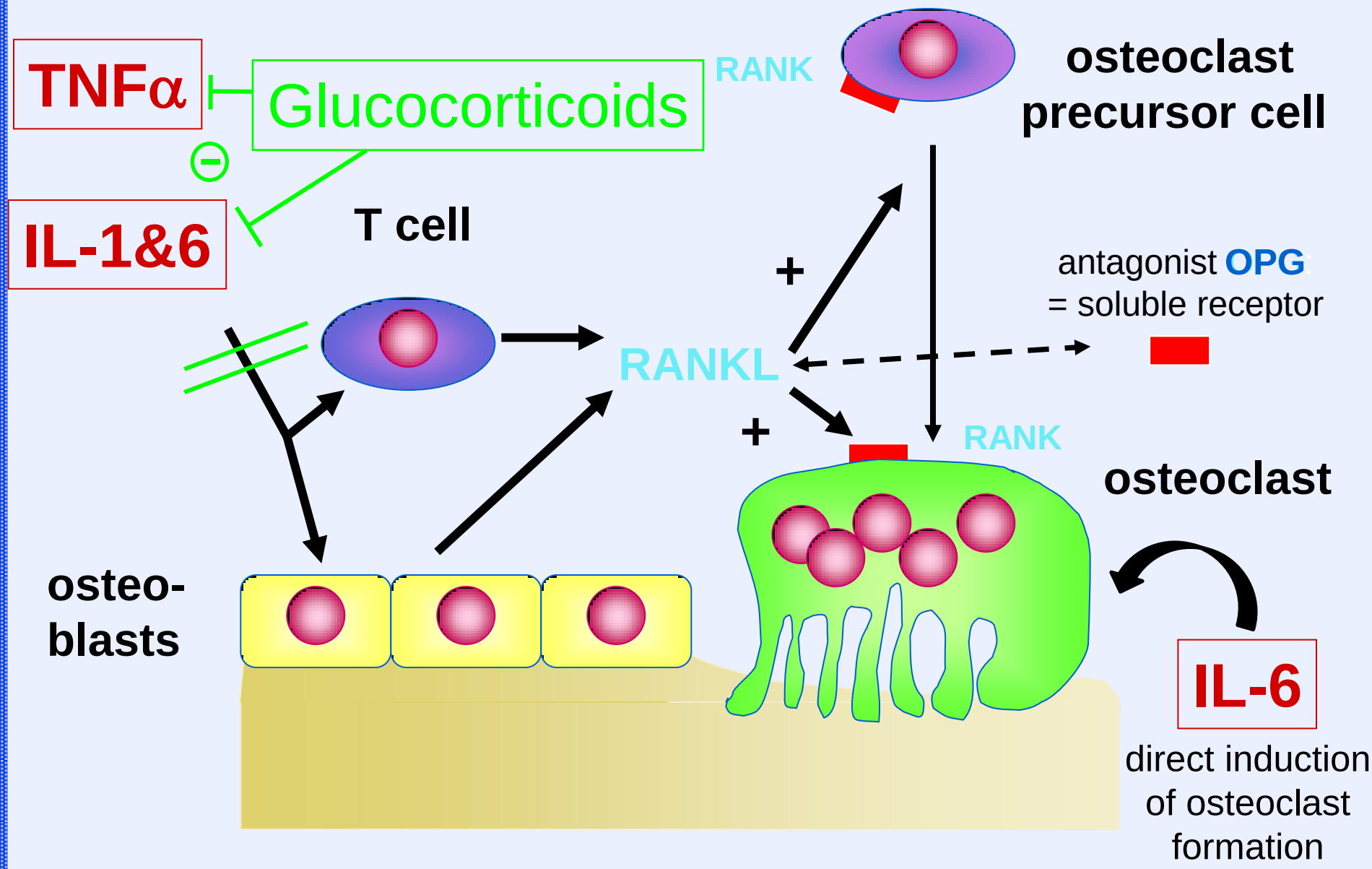
Adapted from Yoshizaki K, *et al*. *Springer Semin Immunopathol* 1998; **20**:247–259.

Articular effects of IL-6 in RA

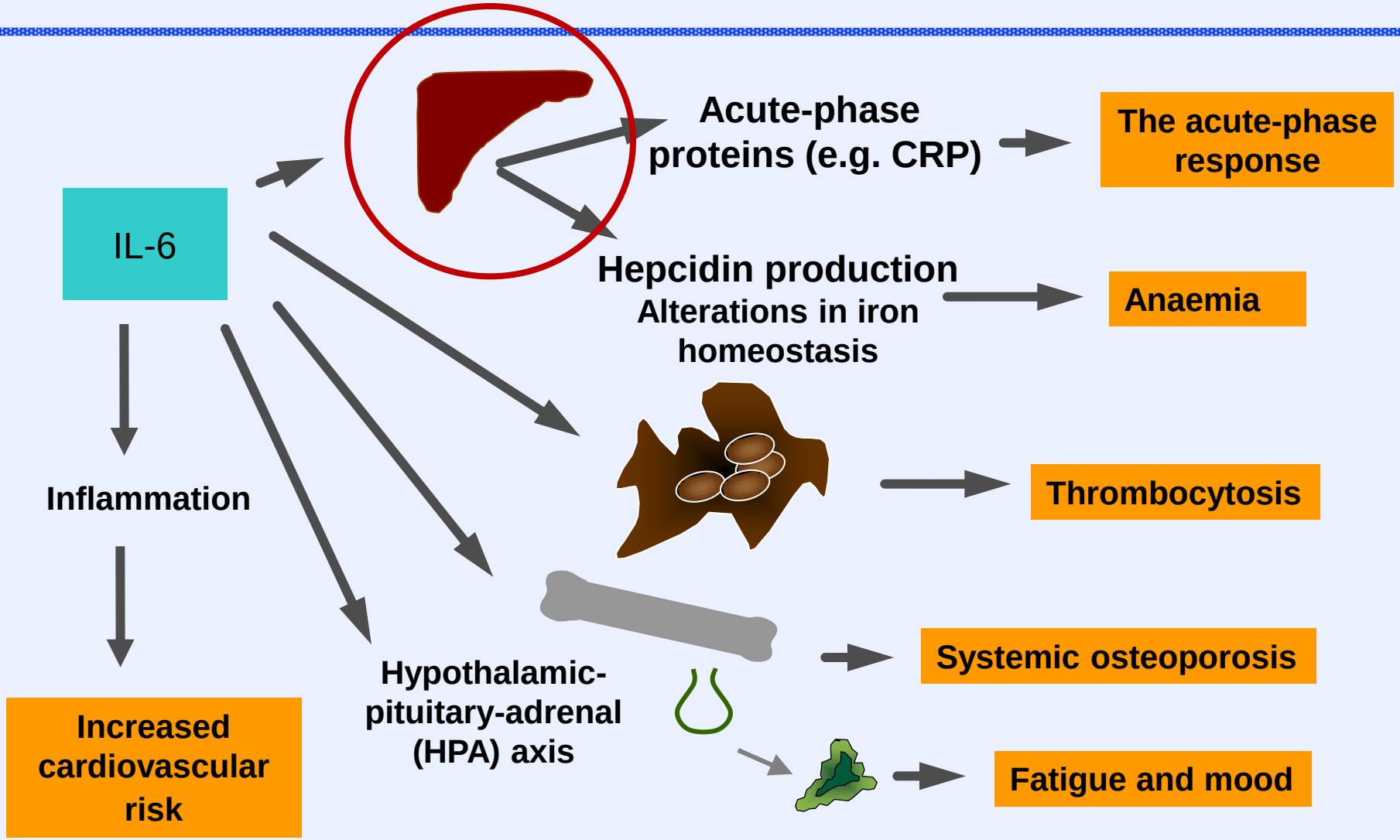


Dayer J-M & Choy E. *Rheumatology* 2010; 49:15–24.
[1]Smolen J, *et al. Nat Rev Drug Disc* 2003; 2:473–488.

TNFα, IL1 & IL6 induce bone resorption

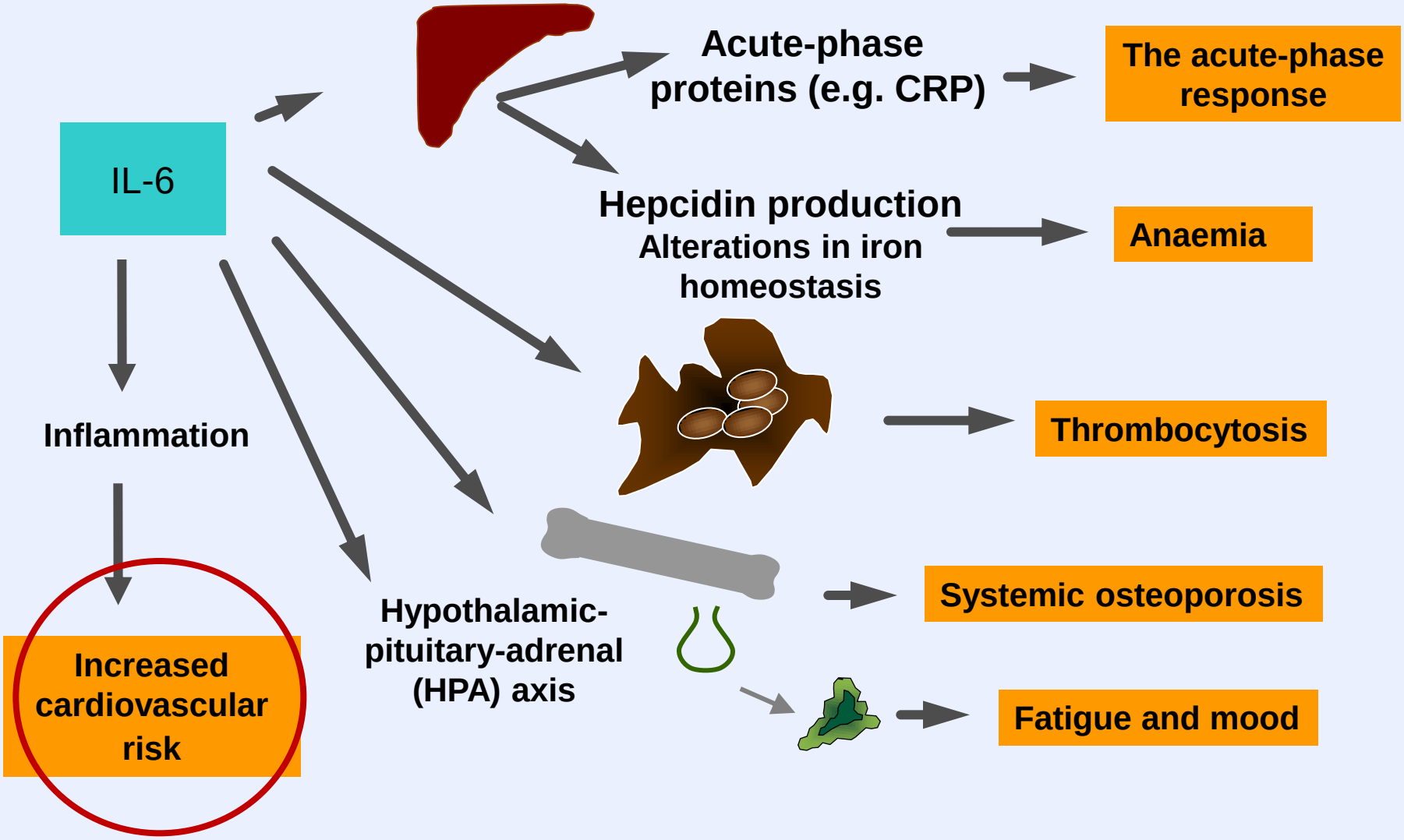


Systemic effects of IL-6 in RA

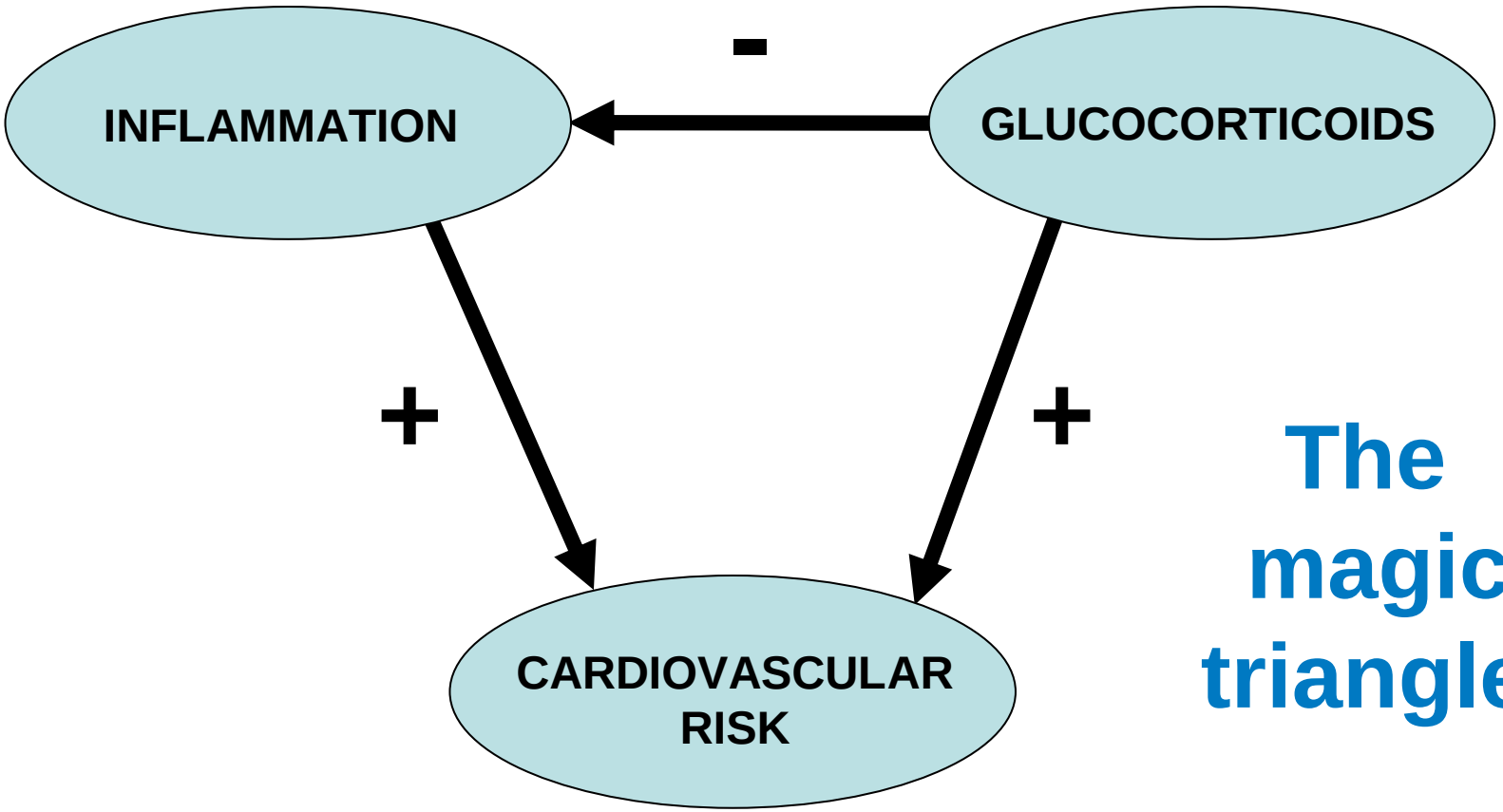


Dayer J-M & Choy E. *Rheumatology* 2010; 49:15–24.

Systemic effects of IL-6 in RA



Dayer J-M & Choy E. *Rheumatology* 2010; 49:15–24.



The magic triangle

Inflammation, glucocorticoids and risk of cardiovascular disease

Frank Buttgereit*, Gerd-Rüdiger Burmester and Brian J Lipworth

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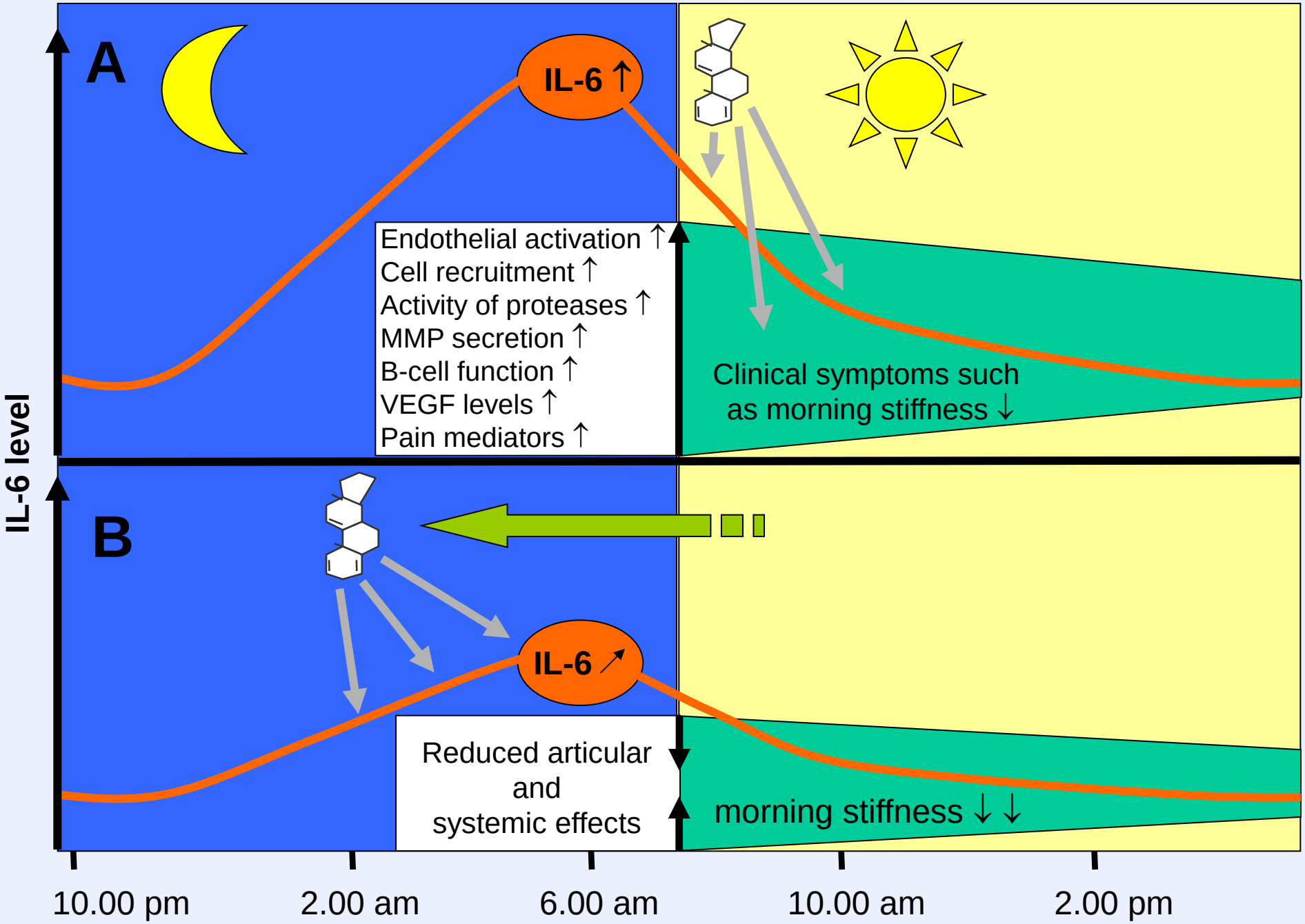
Agenda

Interleukin 6 (IL-6)

- Biological activities & effects in rheumatoid arthritis (RA)
- IL-6 inhibition for the treatment of RA, polymyalgia rheumatica (PMR) and giant cell arteritis (GCA)

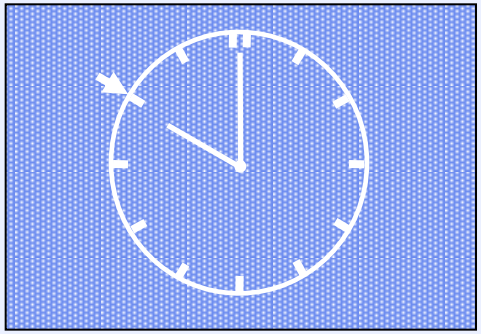
Modified-release prednisone

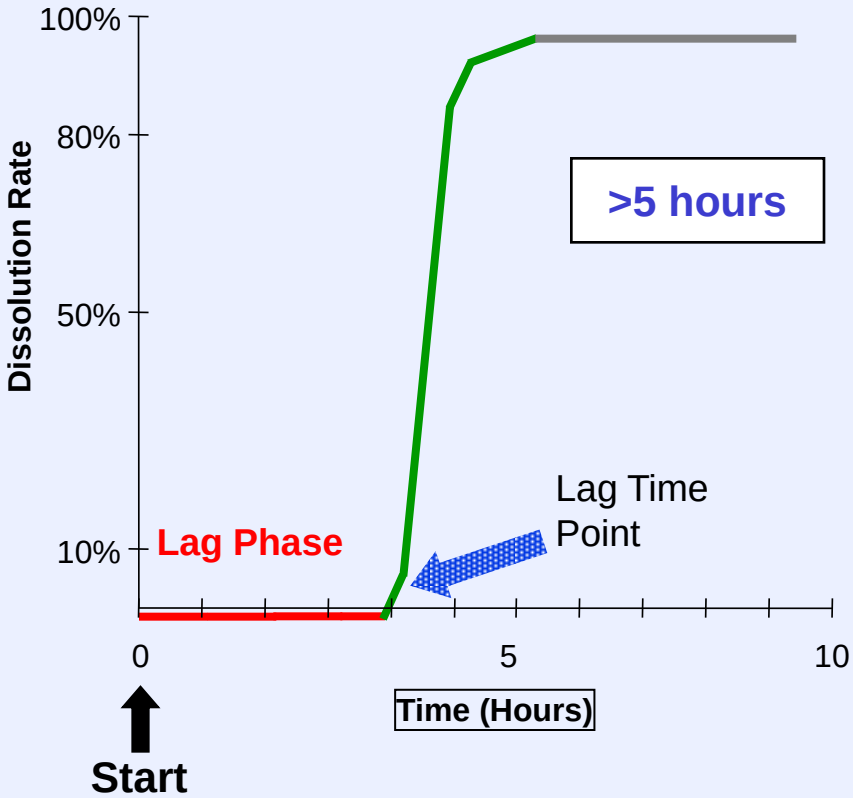
Buttgereit F, *et al*. *Lancet* 2008,
***Ann Rheum Dis* 2010 & 2013**



Buttgereit et al. Arthritis Rheum (2011)

MR Prednisone (modified release): Design





Shell, Prednisone Starts
Air Bubbles

Overview of phase III clinical studies in rheumatoid arthritis: CAPRA-1 (+ extension) and CAPRA-2

	CAPRA-1[1]	CAPRA-1 extension[2]	CAPRA-2[3]
Design	Randomised Double-blind Double-dummy Active control	Open label	Randomised Double-blind Placebo-controlled
Patients	On stable low-dose GC (2.5–10mg/day) Stable DMARD allowed	From CAPRA-1	Not on GC Stable DMARD allowed
Study treatments	Continue same dose conventional prednisone (morning dose) OR Same dose modified-release prednisone (evening dose)	All patients continue on stable dose, taken as modified-release prednisone (evening dose)	Placebo OR Modified-release prednisone 5mg/day (both evening doses)
1° endpoint	Change in duration of morning stiffness		ACR20 response
Duration	12 weeks	9 months	12 weeks

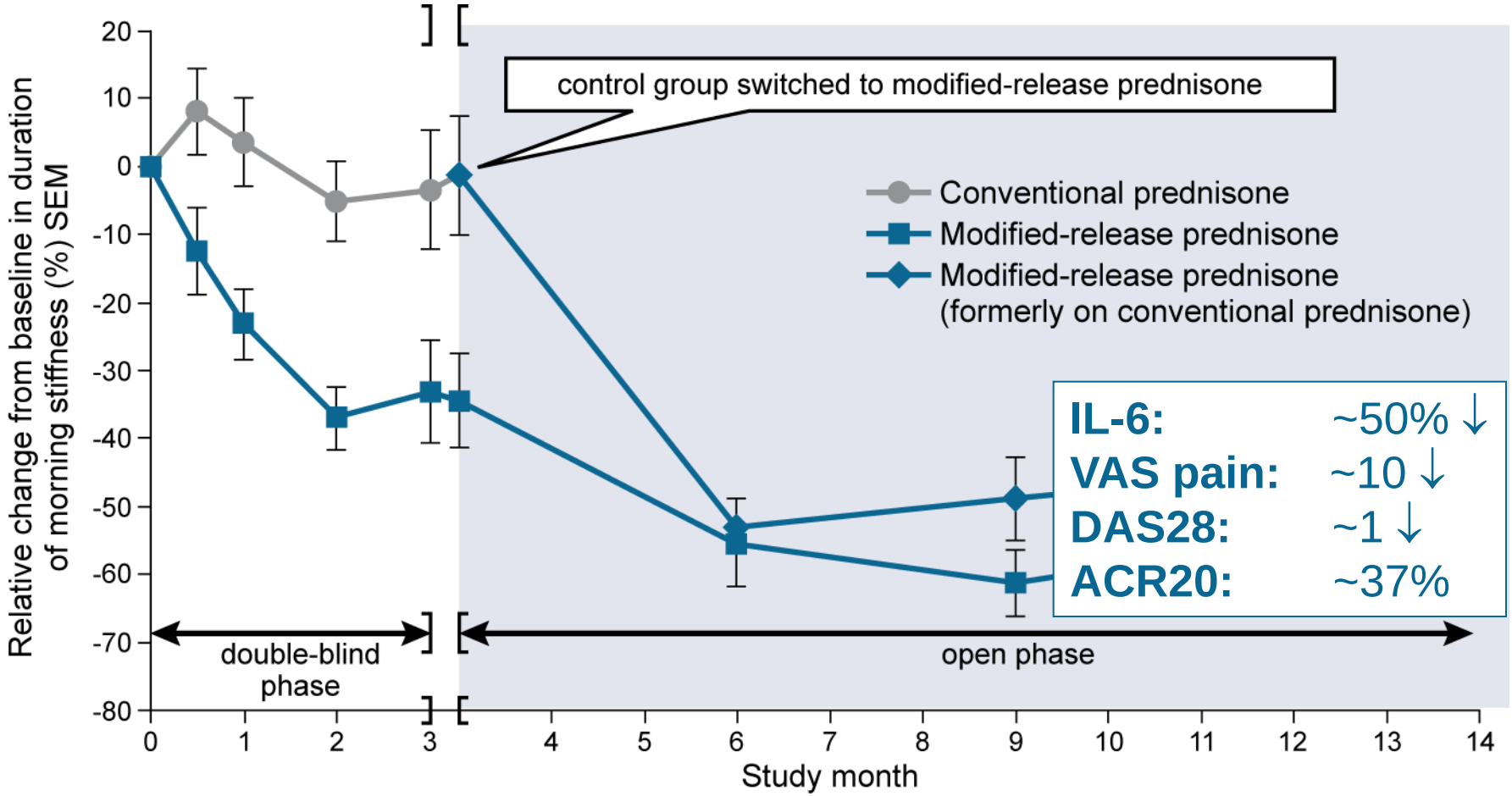
CAPRA, circadian administration of prednisone in rheumatoid arthritis; GC, glucocorticoid; DMARD, disease-modifying anti-rheumatic drug

1. Buttgereit et al. Lancet (2008)
2. Buttgereit et al. Ann Rheum Dis (2010)
3. Buttgereit et al. Ann Rheum Dis (2013)

CAPRA-1: Results (db phase & open follow-up)

Sustained Reduction in Morning Stiffness

Duration of Morning Stiffness: Relative Change from Baseline (ITT)



IL-6: ~50% ↓
VAS pain: ~10 ↓
DAS28: ~1 ↓
ACR20: ~37%

Buttgereit et al., Lancet (2008)

Buttgereit et al., Ann Rheum Dis (2010)

CAPRA-1 extension: change from baseline in secondary endpoints after prolonged treatment

Significant improvement from baseline in IL-6 levels, pain scores and DAS28 after treatment with modified-release prednisone in the evening for up to 12 months

	Modified-release prednisone		Switched to modified-release prednisone ¶	
	Baseline (N=144)	**12 months (N=104)**	**Baseline (N=144)**	**12 months (N=115)**
Median IL-6 (range), units/L	860 (200-23000)	**470 *** (200-18300)	1110 (200-20800)	**515 *** (200-8100)
Mean pain VAS (SD), mm	51 (15)	**40 *** (26)	52 (17)	**39 *** (24)
Mean DAS28 (SD)	5.8 (0.8)	**4.8 *** (1.3)	5.9 (0.9)	**4.9 *** (1.2)
% ACR20 (n)	n.a.	**37.5** (39)	n.a.	**37.4** (43)

* Descriptive p-values: $p<0.05$

¶ Switched from conventional prednisone to open-label modified-release prednisone at end of double-blind period (12 weeks) so received modified-release prednisone for 9 months

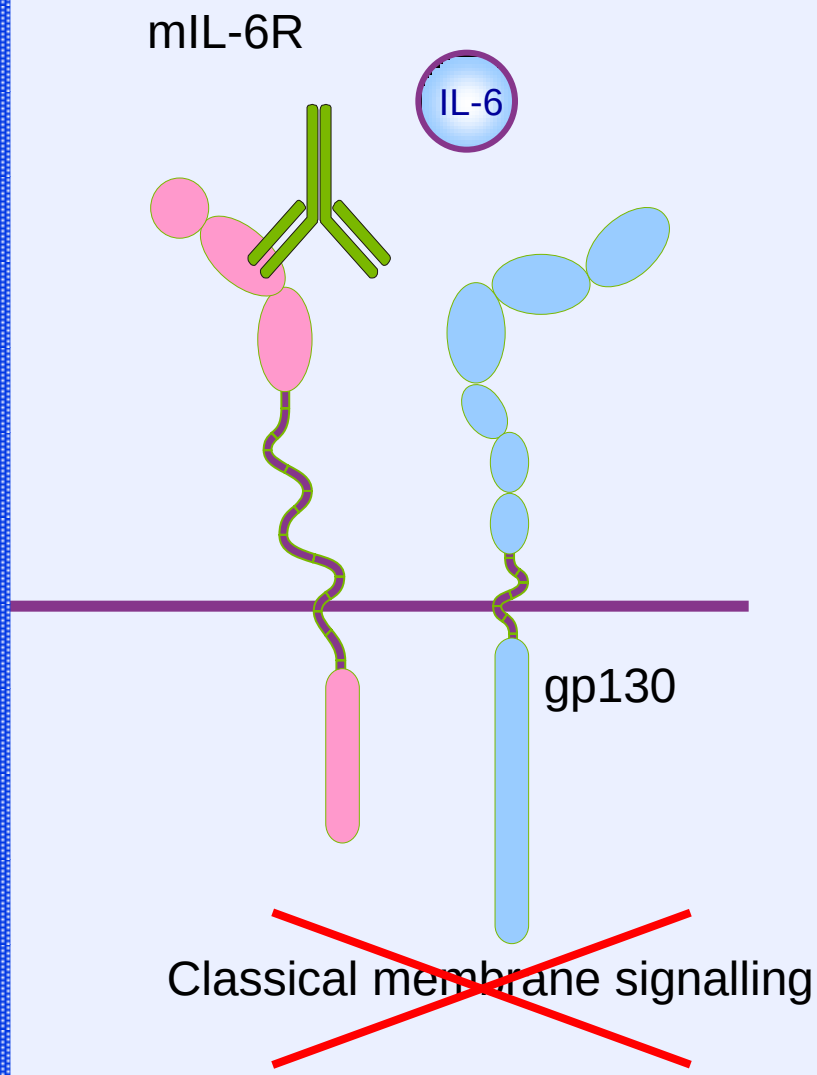
Buttgereit et al., Ann Rheum Dis (2010)

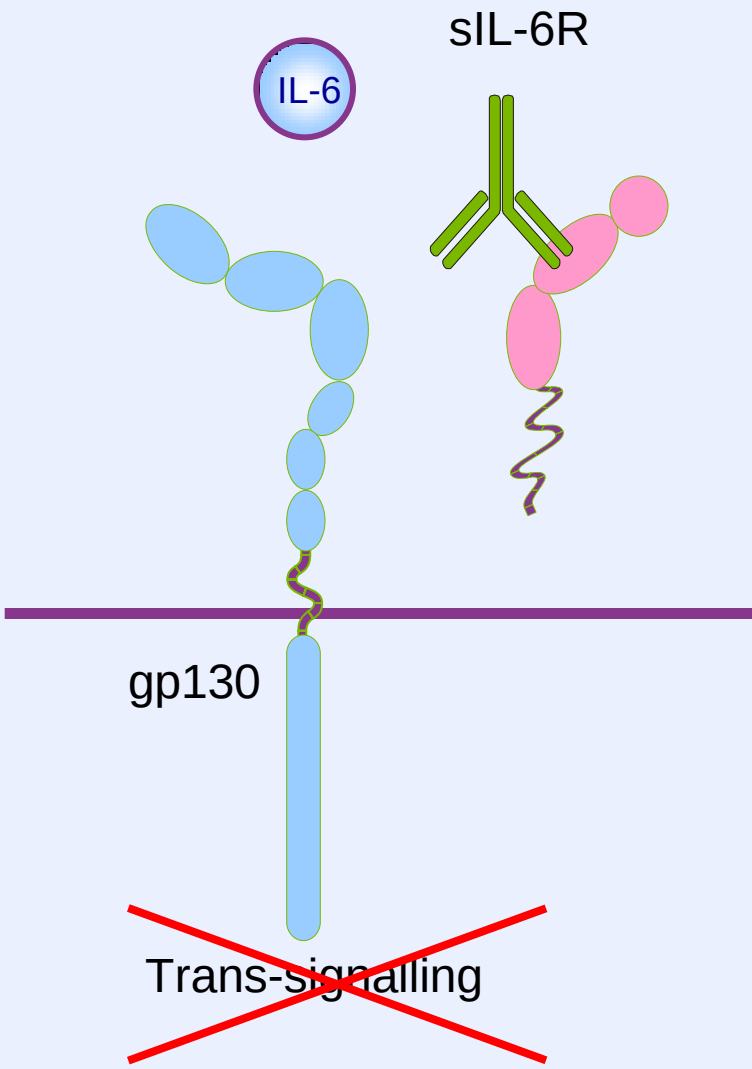
Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMACTA)

Burmester GR, Rubbert-Roth A, Cantagrel A, *et al*.

***Ann Rheum Dis*. 2016, 75, 68-74**

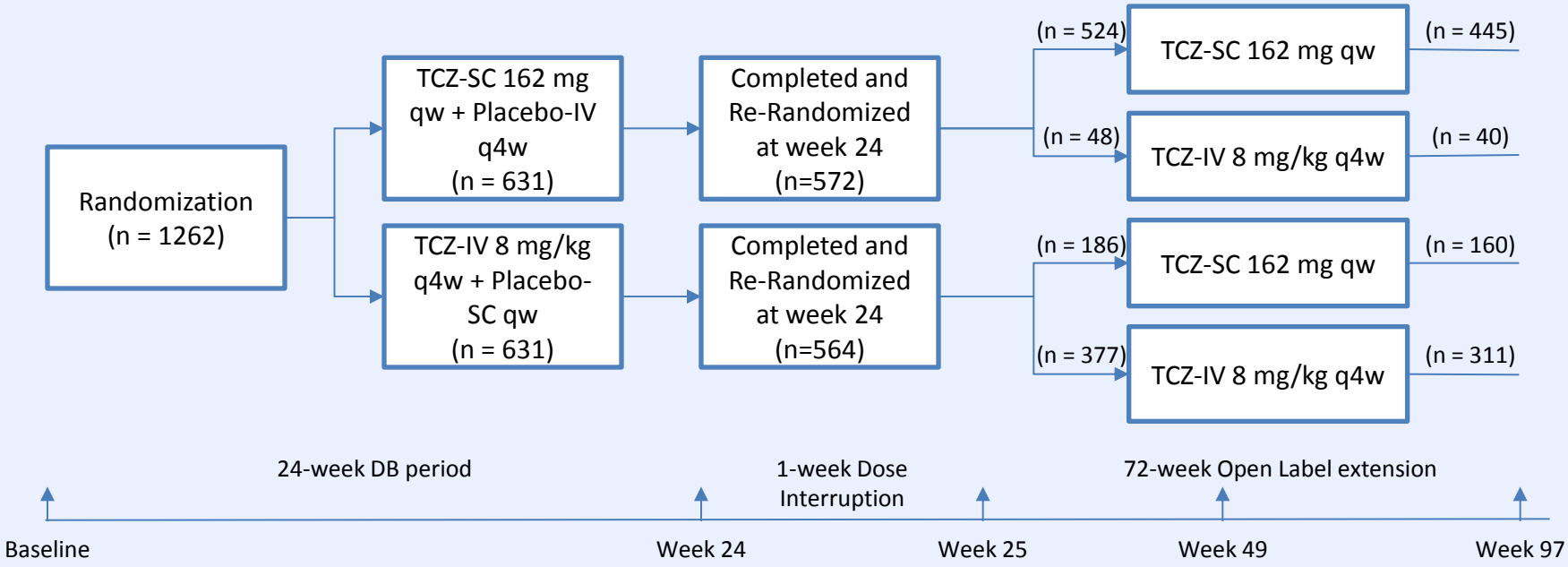
Tocilizumab is a humanised anti-IL-6R monoclonal antibody that inhibits IL-6R signalling





Mihara M, *et al. Int Immunopharmacol* 2005; 5:1731–1740.

SUMMACTA: Study design



All patients received ≥1 dose of study drug and were eligible for inclusion in the intent-to-treat and safety populations

Burmester GR, Rubbert-Roth A, Cantagrel A, *et al. Ann Rheum Dis.* 10 May 2015. [Epub ahead of print]

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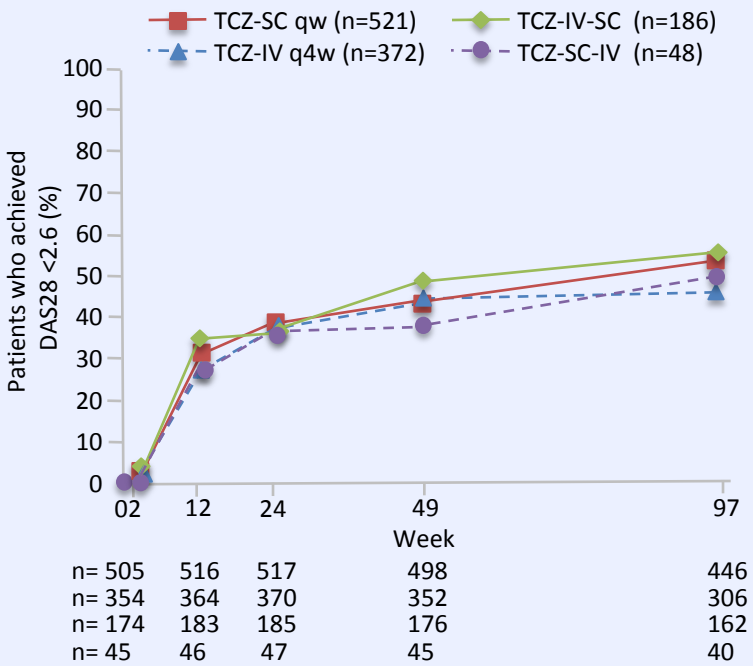
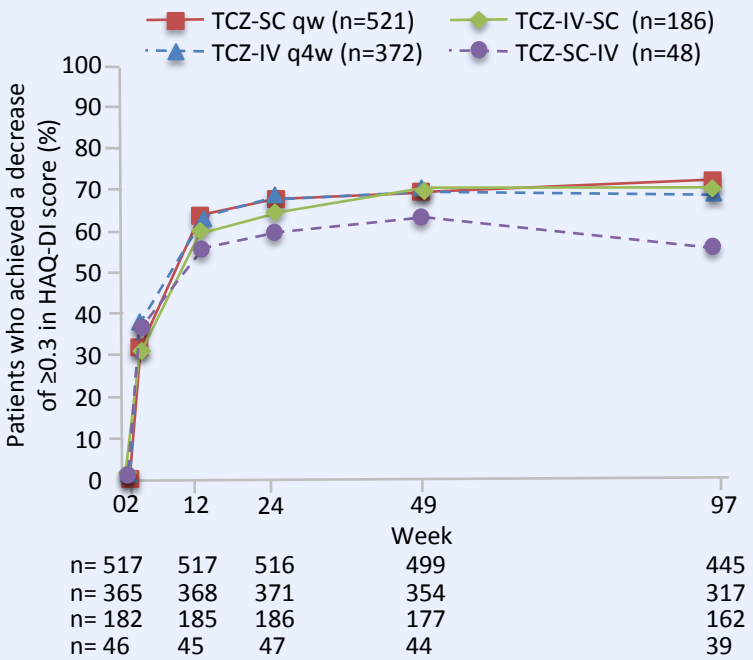
Cytokine Signalling Forum

SUMMACTA: Results

DAS28 remission and HAQ-DI response





The proportion of patients retaining DAS28 remission was similar in all groups at week 24 and was maintained to week 97. The proportions of patients who achieved HAQ-DI response at week 97 were comparable between TCZ-SC and TCZ-IV arms

Burmester GR, Rubbert-Roth A, Cantagrel A, *et al. Ann Rheum Dis.* 10 May 2015. [Epub ahead of print]

CSF
Cytokine Signalling Forum

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Review

Polymyalgia Rheumatica and Giant Cell Arteritis
A Systematic Review

Frank Buttgereit, MD; Christian Dejaco, MD, PhD; Eric L. Matteson, MD, MPH; Bhaskar Dasgupta, MD

IMPORTANCE Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are related inflammatory disorders occurring in persons aged 50 years and older. Diagnostic and therapeutic approaches are heterogeneous in clinical practice.

OBJECTIVE To summarize current evidence regarding optimal methods for diagnosing and treating PMR and GCA.

EVIDENCE REVIEW MEDLINE, EMBASE, and Cochrane databases were searched from their inception dates to March 30, 2016. Screening by 2 authors resulted in 6626 abstracts, of which 50 articles met the inclusion criteria. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool or American College of Cardiology Foundation/American Heart Association methodology.

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com

Published
14th of June 2016

JAMA. 2016;315(22):2442-2458. doi:10.1001/jama.2016.5444

FINDINGS Twenty randomized clinical trials for therapy (n = 1016 participants) and 30 imaging studies for diagnosis and/or assessing response to therapy (n = 2080 participants) were included. The diagnosis of PMR is based on clinical features such as new-onset bilateral shoulder pain, including subdeltoid bursitis, muscle or joint stiffness, and functional impairment. Headache and visual disturbances including loss of vision are characteristic of GCA. Constitutional symptoms and elevated inflammatory markers (>90%) are common in both diseases. Ultrasound imaging enables detection of bilateral subdeltoid bursitis in 69% of PMR patients. In GCA, temporal artery biopsy remains the standard for definitive diagnosis. Ultrasound and magnetic resonance imaging (MRI) of large vessels revealing inflammation-induced wall thickening support the diagnosis of GCA (specificity 78%-100% for ultrasound and 73%-97% for MRI). Glucocorticoids remain the primary treatment, but the optimal initial dose and tapering treatment regimens are unknown. According to consensus-based recommendations, initial therapy for PMR is prednisone, 12.5 to 25 mg/day or equivalent, and 40 to 60 mg/day for GCA, followed by individualized tapering regimens in both diseases. Adjunctive methotrexate may reduce cumulative glucocorticoid dosage by 20% to 44% and relapses by 36% to 54% in both PMR and GCA. Use of tocilizumab as additional treatment with prednisone showed a 2- to 4-fold increase in remission rates of GCA in a randomized clinical trial (N = 30).

CONCLUSIONS AND RELEVANCE Diagnosis of PMR/GCA is made by clinical features and elevated inflammatory markers. In PMR, ultrasound imaging may improve diagnostic accuracy. In GCA, temporal artery biopsy may not be required in patients with typical disease features accompanied by characteristic ultrasound or MRI findings. Consensus-based recommendations suggest glucocorticoids as the most effective therapy for PMR/GCA. Methotrexate may be added to glucocorticoids in patients at risk for relapse and in those with glucocorticoid-related adverse effects or need for prolonged glucocorticoid therapy.

Anti-inflammatory and immunosuppressive actions of glucocorticoids

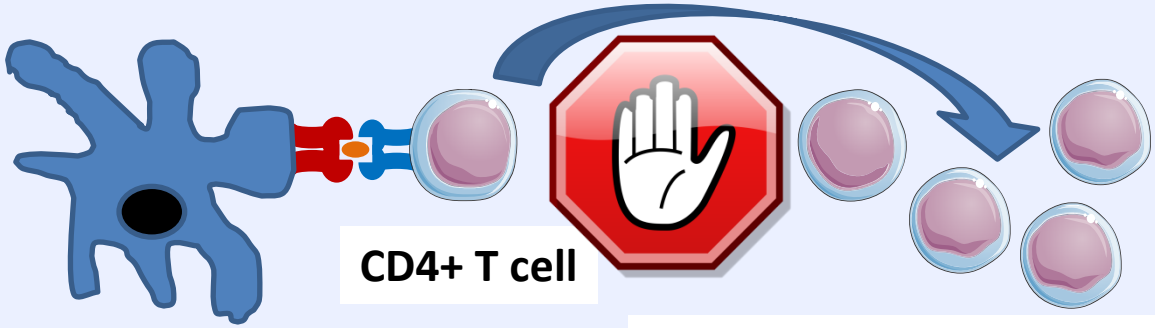
… in giant cell arteritis

Unknown antigen
(e.g. virus / bacteria)

Environmental factors
(e.g. smoking)

Genetic risk factors
(e.g. HLA DRB1*01 / *04 genotypes

Vascular / immune aging



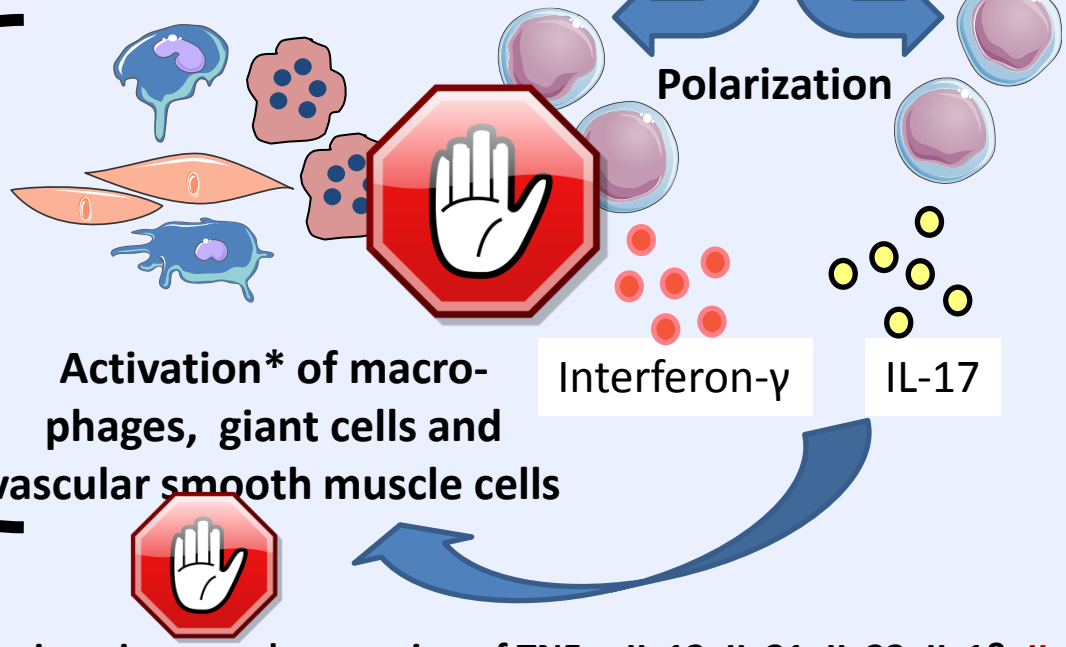
Mature dendritic cells present the antigen to T cells

T cell activation* and proliferation in the adventitia

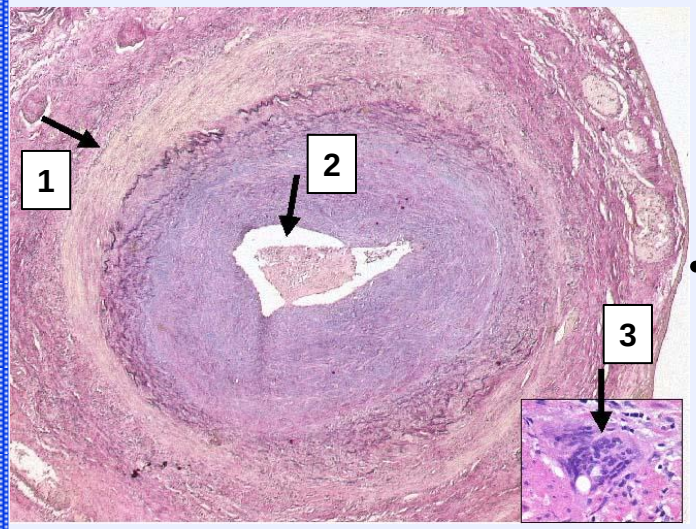
Th1 cells

Th17 cells

Polarization

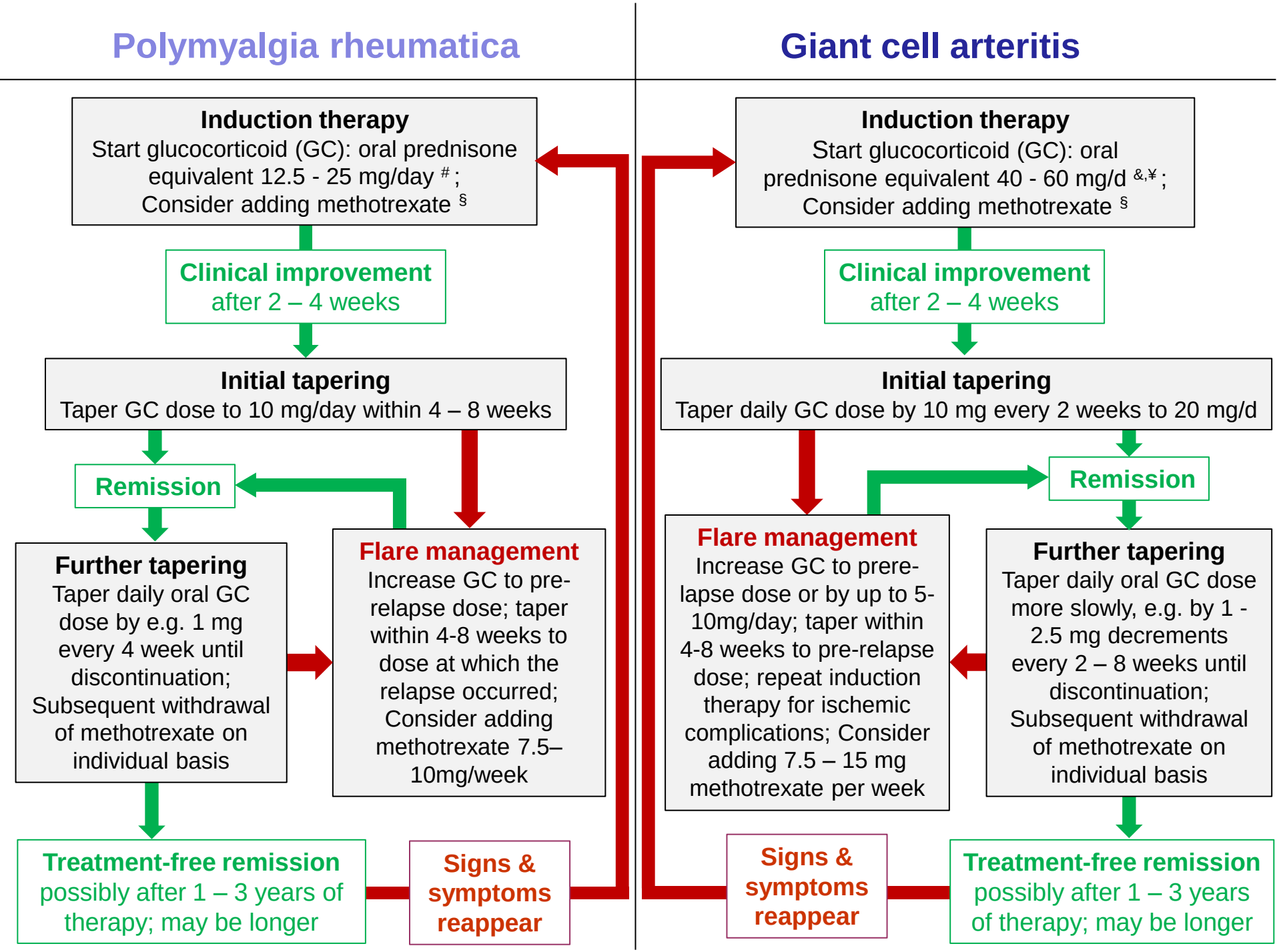


Activation* of macro-phages, giant cells and vascular smooth muscle cells



Vascular remodeling:
1 Inflammatory wall thickening
2 Decreased luminal diameter
3 Multinucleated giant cell

* There is an increased expression of TNFα, IL-12, IL-21, IL-23, IL-1β, IL-6 and other cytokines by activated immune cells. Especially IL-1β and IL-6 are considered important causes of the systemic manifestations.


Polymyalgia rheumatica
Giant cell arteritis
Induction therapy
Start glucocorticoid (GC): oral prednisone equivalent 12.5 - 25 mg/day #;
Consider adding methotrexate §
Clinical improvement
after 2 – 4 weeks
Initial tapering
Taper GC dose to 10 mg/day within 4 – 8 weeks
Remission
Further tapering
Taper daily oral GC dose by e.g. 1 mg every 4 week until discontinuation;
Subsequent withdrawal of methotrexate on individual basis
Flare management
Increase GC to pre-relapse dose; taper within 4-8 weeks to dose at which the relapse occurred;
Consider adding methotrexate 7.5–10mg/week
Treatment-free remission
possibly after 1 – 3 years of therapy; may be longer
Signs & symptoms reappear
Induction therapy
Start glucocorticoid (GC): oral prednisone equivalent 40 - 60 mg/d &,¥;
Consider adding methotrexate §
Clinical improvement
after 2 – 4 weeks
Initial tapering
Taper daily GC dose by 10 mg every 2 weeks to 20 mg/d
Remission
Flare management
Increase GC to prere-lapse dose or by up to 5-10mg/day; taper within 4-8 weeks to pre-relapse dose; repeat induction therapy for ischemic complications; Consider adding 7.5 – 15 mg methotrexate per week
Further tapering
Taper daily oral GC dose more slowly, e.g. by 1 - 2.5 mg decrements every 2 – 8 weeks until discontinuation;
Subsequent withdrawal of methotrexate on individual basis
Signs & symptoms reappear
Treatment-free remission
possibly after 1 – 3 years of therapy; may be longer

FINDINGS Twenty randomized clinical trials for therapy (n = 1016 participants) and 30 imaging studies for diagnosis and/or assessing response to therapy (n = 2080 participants) were included. The diagnosis of PMR is based on clinical features such as new-onset bilateral shoulder pain, including subdeltoid bursitis, muscle or joint stiffness, and functional impairment. Headache and visual disturbances including loss of vision are characteristic of GCA. Constitutional symptoms and elevated inflammatory markers (>90%) are common in both diseases. Ultrasound imaging enables detection of bilateral subdeltoid bursitis in 69% of PMR patients. In GCA, temporal artery biopsy remains the standard for definitive diagnosis. Ultrasound and magnetic resonance imaging (MRI) of large vessels revealing inflammation-induced wall thickening support the diagnosis of GCA (specificity 78%-100% for ultrasound and 73%-97% for MRI). Glucocorticoids remain the primary treatment, but the optimal initial dose and tapering treatment regimens are unknown. According to consensus-based recommendations, initial therapy for PMR is prednisone, 12.5 to 25 mg/day or equivalent, and 40 to 60 mg/day for GCA, followed by individualized tapering regimens in both diseases. Adjunctive methotrexate may reduce cumulative glucocorticoid dosage by 20% to 44% and relapses by 36% to 54% in both PMR and GCA. Use of tocilizumab as additional treatment with prednisone showed a 2- to 4-fold increase in remission rates of GCA in a randomized clinical trial (N = 30).

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Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial

www.thelancet.com Published online March 4, 2016

Peter M Villiger, Sabine Adler*, Stefan Kuchen, Felix Wermelinger, Diana Dan, Veronika Fiege, Lukas Bütikofer, Michael Seitz, Stephan Reichenbach*

Summary

Background Giant cell arteritis is an immune-mediated disease of medium and large-sized arteries that affects mostly people older than 50 years of age. Treatment with glucocorticoids is the gold-standard and prevents severe vascular complications but is associated with substantial morbidity and mortality. Tocilizumab, a humanised monoclonal antibody against the interleukin-6 receptor, has been associated with rapid induction and maintenance of remission in patients with giant cell arteritis. We therefore aimed to study the efficacy and safety of tocilizumab in the first randomised clinical trial in patients with newly diagnosed or recurrent giant cell arteritis.

Methods In this single centre, phase 2, randomised, double-blind, placebo-controlled trial, we recruited patients aged 50 years and older from University Hospital Bern, Switzerland, who met the 1990 American College of Rheumatology criteria for giant cell arteritis. Patients with new-onset or relapsing disease were randomly assigned (2:1) to receive either tocilizumab (8 mg/kg) or placebo intravenously. 13 infusions were given in 4 week intervals until week 52. Both groups received oral prednisolone, starting at 1 mg/kg per day and tapered down to 0 mg according to a standard reduction scheme defined in the study protocol. Allocation to treatment groups was done using a central computerised randomisation procedure with a permuted block design and a block size of three, and concealed using central randomisation generated by the clinical trials unit. Patients, investigators, and study personnel were masked to treatment assignment. The primary outcome was the proportion of patients who achieved complete remission of disease at a prednisolone dose of 0·1 mg/kg per day at week 12. All analyses were intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01450137.

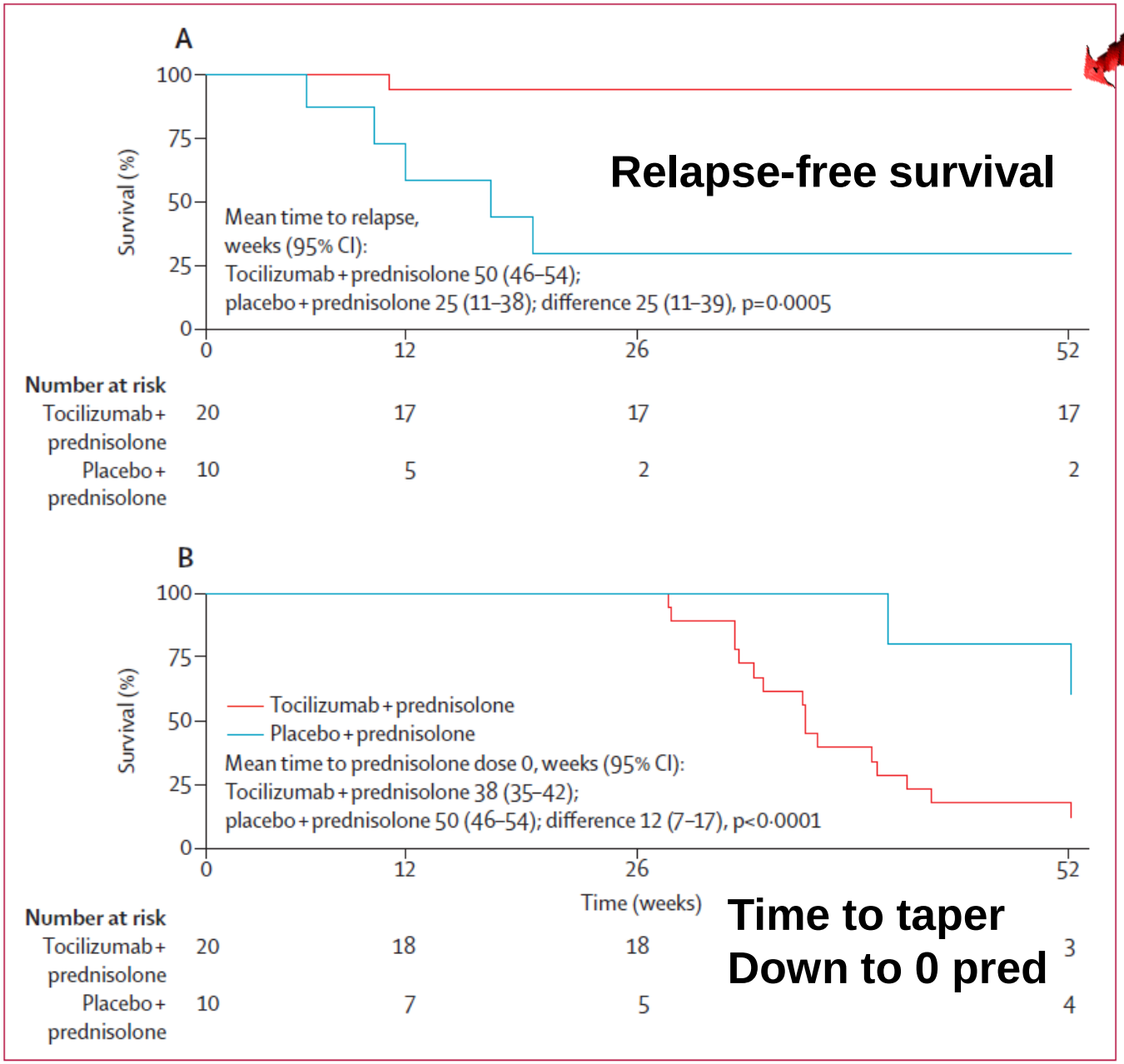
Villiger et al., Lancet 2016

Methods:

Single center, phase 2, double-blind RCT; GCA patients randomly assigned (2:1) to TCZ iv (8 mg/kg) + GC or placebo iv (PBO) + GC; 13 infusions in 4 wk intervals until wk 52;
GC initially 1 mg/kg/d → 0.1 mg/kg/d at week 12
Further tapering down to 0 (defined reduction scheme)

Results:

(1) 20 patients with TCZ/Pred; 10 with PBO/Pred; 70% female
(2) Complete remission at wk 12: 17/20 (85%) vs. 4/10 (40%)
(3) Relapse-free survival at wk 52: 17/20 (85%) vs. 2/10 (20%)
(4) GC could be earlier stopped in the TCZ/Pred group
= significantly lower cumulative GC dose
(5) SAEs: 35% (TCZ) and 50% (PBO)



TCZ + Pred

PBO + Pred

PBO + Pred

TCZ + Pred

Interpretation Our findings show, for the first time in a trial setting, the efficacy of tocilizumab in the induction and maintenance of remission in patients with giant cell arteritis.

Tocilizumab

Devauchelle-Pensec V, *et al*. *Lancet* 2016,

MR prednisone

Cutolo M, Buttgereit F, et al. *ACR 2015, Abstract*

… in polymyalgia rheumatica

CONCISE REPORT

Efficacy of first-line tocilizumab therapy in early polymyalgia rheumatica: a prospective longitudinal study

Devauchelle-Pensec V, *et al*. *Ann Rheum Dis* 2016

Valérie Devauchelle-Pensec,[1,2] Jean Marie Berthelot,[3] Divi Cornec,[1,2] Yves Renaudineau,[2] Thierry Marhadour,[1] Sandrine Jousse-Joulin,[1,2] Solène Querellou,[4] Florent Garrigues,[5] Michel De Bandt,[6] Maelenn Gouillou,[7] Alain Saraux[1,2]

ABSTRACT

Background Glucocorticoids are the cornerstone treatment of polymyalgia rheumatica (PMR) but induce adverse events.

Objectives To evaluate the efficacy and safety of first-line tocilizumab in PMR.

Methods In a prospective open-label study (ClinicalTrials.gov: NCT01713842), 20 glucocorticoid-free patients fulfilling Chuang's PMR criteria, with symptom onset within the last 12 months and a PMR activity score (PMR-AS) >10, each received three tocilizumab infusions at 4-week intervals, without glucocorticoids, followed by oral prednisone from weeks 12 to 24 (0.15 mg/kg if PMR-AS ≤10 and 0.30 mg/kg otherwise). The primary end point was the proportion of patients with PMR-AS≤10 at week 12.

Results Baseline median PMR-AS was 36.6 (IQR 30.4–43.8). At week 12, all patients had PMR-AS≤10 and received the low prednisone dosage. Median PMR-AS at weeks 12 and 24 was 4.5 (3.2–6.8) and 0.95 (IQR 0.4–2), respectively ($p<0.001$ vs baseline for both time points). No patient required rescue treatment. Positron emission tomography-CT showed significant improvements. The most common adverse events were transient neutropenia (n=3) and leucopenia (n=5); in one patient, the second tocilizumab infusion was omitted due to leucopenia.

Conclusions Tocilizumab monotherapy is effective in recent-onset PMR. Randomised controlled trials are warranted.

Trial registration number NCT01713842.

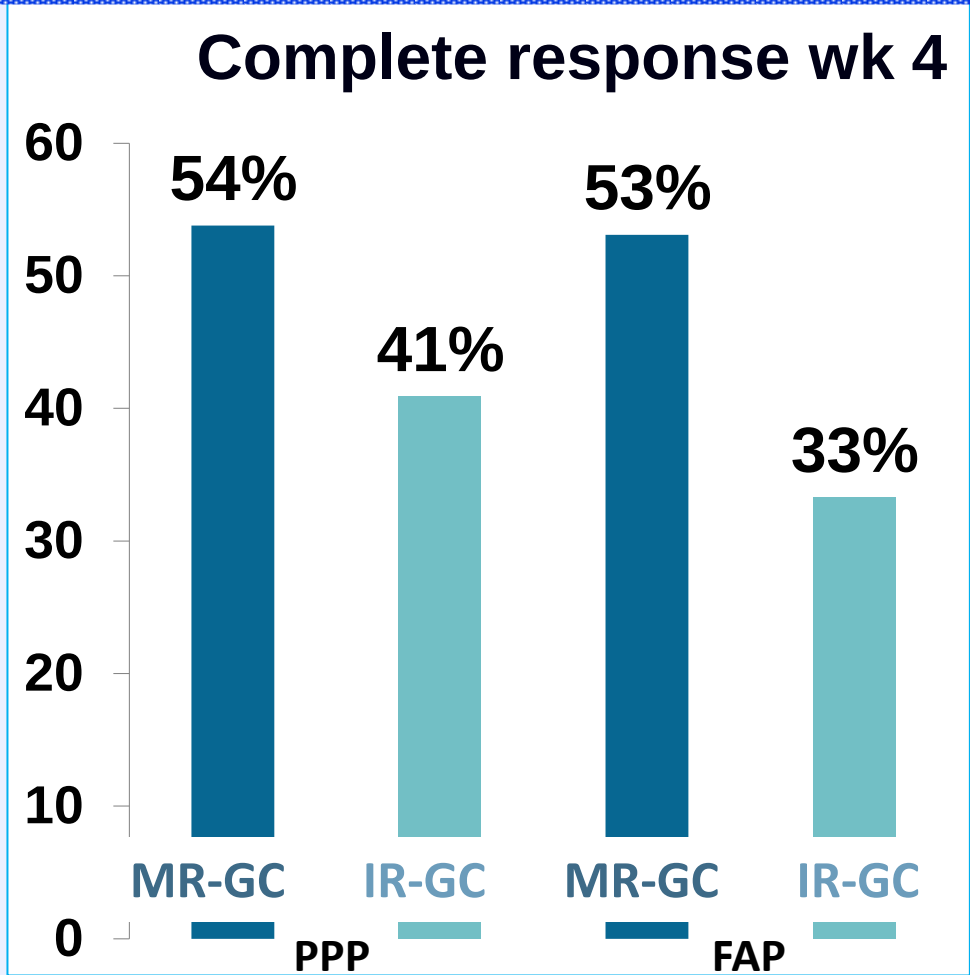
M. Cutolo, M. Hopp, S. Liebscher, B. Dasgupta & F. Buttgereit
Abstract 52101, presented at ACR on Nov, 10th 2015:

MR Prednisone:
Multicenter, Randomized, Phase 3 Study in PMR

- 62 (400 planned) new patients with PMR
- 15mg/d MR Prednisone vs. 15mg/d IR Predni-sone, 4 weeks

Primary outcome:

- % complete responder, >70% improvement of pain, MST, CRP



Thank you !

CHARITÉ CAMPUS MITTE